

### AMENDMENTS TO THE SPECIFICATION

Delete the Existing Sequence Listing and insert the accompanying Sequence Listing (pages 1-141).

At page 18, amend paragraph 0061 as follows:

[0061] Another example of algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described in Altschul *et al.* (1990) *J. Mol. Biol.* 215: 403-410. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/>). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al, supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are then extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, M=5, N=-4, and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength (W) of 3, an expectation (E) of 10, and the BLOSUM62 scoring matrix (*see* Henikoff & Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915).

At page 34, amend paragraph 0117 as follows:

[0117] The protective function of the D peptides of this invention is illustrated in the parent applications (09/645,454, filed August 24, 2000, now U.S. Patent 6,664,230, 09/896,841, filed June 29,

2001, now U.S. Patent 6,933,270, and WO 02/15923 (PCT/US01/26497), filed June 29, 2001, *see, e.g.*, Figures 1-5 in WO 02/15923]. Figure 1, panels A, B, C, and D in WO 02/15923 show the association of  $^{14}\text{C}$ -D-5F with blood components in an ApoE null mouse. It is also demonstrated that HDL from mice that were fed an atherogenic diet and injected with PBS failed to inhibit the oxidation of human LDL and failed to inhibit LDL-induced monocyte chemotactic activity in human artery wall cocultures. In contrast, HDL from mice fed an atherogenic diet and injected daily with peptides described herein was as effective in inhibiting human LDL oxidation and preventing LDL-induced monocyte chemotactic activity in the cocultures as was normal human HDL (Figures 2A and 2B in WO 02/15923). In addition, LDL taken from mice fed the atherogenic diet and injected daily with PBS was more readily oxidized and more readily induced monocyte chemotactic activity than LDL taken from mice fed the same diet but injected with 20  $\mu\text{g}$  daily of peptide 5F. The D peptide did not appear to be immunogenic (Figure 4 in WO 02/15923).

At page 46, amend paragraph 0153 as follows:

[0153] Longer peptides (*e.g.* up to 10, 11, or 15 amino acids) are also contemplated within the scope of this invention. ~~Typically~~ Typically where the shorter peptides (*e.g.* peptides according to formula I) are characterized by an acidic, basic, aliphatic, or aromatic amino acid, the longer peptides are characterized by acidic, basic, aliphatic, or aromatic domains comprising two or more amino acids of that type.

At page 89, amend paragraph

[0285] Figure 22 shows that SEQ ID NO: 242 and SEQ ID NO: 258 ~~4523242541422382582822438~~ and SEQ ID NO. 203 from Table 4 were equally effective or even more effective than D-4F in reducing the lipid hydroperoxide content of both LDL and HDL in apoE null mice. These data are consistent with D-4F and the peptides described in this application acting in part by sequestering the "seeding molecules" necessary for LDL to induce the inflammatory atherosclerotic reaction. Taken together with the data shown in Figures 3 to 19 it is very likely that the peptides described in this application (*e.g.* SEQ ID NO. 198 and SEQ ID NO. 203 from Table 4) will be as or more effective than D-4F in ameliorating atherosclerosis.

Amend the abstract as follows:

[0287] This invention provides novel peptides for the treatment of ~~that ameliorate one or more symptoms of atherosclerosis.~~ In certain embodiments the peptide is  $X^1-X^2-X^3-X^4$  where  $X^1$  and  $X^4$  are independently selected from the group consisting of alanine (Ala), valine (Val), leucine (Leu), isoleucine (Ile), proline (Pro), phenylalanine (Phe), tryptophan (Trp), methionine (Met), serine (Ser) bearing a hydrophobic protecting group, beta-naphthyl alanine, alpha-naphthyl alanine, norleucine, cyclohexylalanine, threonine (Thr) bearing a hydrophobic protecting group, tyrosine (Tyr) bearing a hydrophobic protecting group, lysine (Lys) bearing a hydrophobic protecting group, arginine (Arg) bearing a hydrophobic protecting group, ornithine (Orn) bearing a hydrophobic protecting group, aspartic acid (Asp) bearing a hydrophobic protecting group, cysteine (Cys) bearing a hydrophobic protecting group, and glutamic acid (Glu) bearing a hydrophobic protecting group;  $X^2$  and  $X^3$  are independently selected from the group consisting of Asp, Arg, and Glu; and the peptide converts pro-inflammatory HDL to anti-inflammatory HDL or makes anti-inflammatory HDL more anti-inflammatory. The peptides are highly stable and readily administered via an oral route. The peptides are effective to stimulate the formation and cycling of pre-beta high density lipoprotein-like particles and/or to promote lipid transport and detoxification. This invention also provides a method of tracking a peptide in a mammal. In addition, the peptides inhibit osteoporosis. When administered with a statin, the peptides enhance the activity of the statin permitting the statin to be used at significantly lower dosages and/or cause the statins to be significantly more anti-inflammatory at any given dose.